REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims fully supported by the specification and claims as originally filed, and do not add new matter. The specification has been amended to delete references to embedded hyperlinks and/or browser-executable code. Further, the paragraph starting on page 374, line 32 of the specification has been amended to comply with the provisions of the Budapest Treaty.

Prior to the present amendment, claims 58-70 were pending in this application. With this amendment, Claims 58-67 have been amended to further clarify what applicants have always regarded as their invention. Support for the amendments to Claims 58-62 is found in the specification at, for example, page 351, lines 18-32, wherein the protocol and results of the chondrocyte re-differentiation assay are described. Support for polypeptides "comprising" polypeptide variants is found in the specification at, for example, page 108, line 38, to page 109, line 26.

Claims 58-70 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants thank the Examiner for entering the preliminary amendments of October 16, 2001, February 15, 2002, and August 21, 2002.

I. Specification

As requested by the PTO, Applicants have reviewed the application and deleted all references to embedded hyperlinks and/or browser-executable code. The ATCC address on page 372, line 34, has been amended and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty. Additionally, the status of the prior US application 09/918,585 (now abandoned) has been updated.

The title of the present application has been amended to clearly indicate the invention to which the claims are directed.

II. Information Disclosure Statement

The Examiner has stated that the BLAST results cited in the Information Disclosure Statement submitted on September 4, 2002, have not been considered because the information on the referred databases is allegedly incomplete. Applicants file herewith an Information

Disclosure Statement listing each reference of the "BLAST Search" separately and including authors/inventors, database names, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

III. Priority

Applicants thank the Examiner for granting the priority date of the instant application as February 18, 2000.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62 and 69-70 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner asserts that "[t]he claims do not require that the polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus the claims are drawn to a genus of molecules that is defined by sequence identity only." (Page 6 of the instant Office Action).

The Examiner has acknowledged that "Applicants have taught the polypeptide of SEQ ID NO:59, and have identified specific amino acids as the signal sequence (amino acids 1-16) and the transmembrane domain (amino acids 232-251)." (Page 8 of the instant Office Action). As is known in the art, and defined in the specification, the extracellular domain of a protein is the region from the amino terminus to the beginning of the transmembrane domain (see page 122, lines 12-14 of the specification). Thus the specification clearly describes the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, the extracellular domain of the polypeptide of SEQ ID NO:59, and the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide.

Without acquiescing to the Examiner's position, Applicants submit that Claims 58-62, as amended herein, recite polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:59, the polypeptide of SEQ ID NO:59 lacking its associated signal peptide, the extracellular domain of the polypeptide of SEQ ID NO:59, and the extracellular domain of the polypeptide of SEQ ID NO:59, lacking its associated signal peptide, wherein said polypeptide induces chondrocyte re-differentiation. Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By

following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO363 polypeptide induces chondrocyte re-differentiation.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO363 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

As noted by the Examiner, factors to be considered in evidencing possession of a claimed genus include "disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (Page 6 of the instant Office Action). As discussed above, Applicants have recited structural features, namely, 80% sequence identity to the polypeptide of SEQ ID NO:59, which are common to the genus. Applicants have also provided guidance as to how to make the recited variants of SEQ ID NO:59, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity, ability to induce chondrocyte re-differentiation. Accordingly, a description of the claimed genus has been achieved.

Therefore, withdrawal of the written description rejection of Claims 58-62 and 69-70 under 35 U.S.C. §112, first paragraph, is respectfully requested.

V. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 58-62 and 69-70 are rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, while being enabling for the isolated polypeptide that is SEQ ID NO:59, does not reasonably provide enablement for a polynucleotide encoding a polypeptide not

identical to SEQ ID NO:59, as well as a non-isolated cell comprising the polynucleotide." (Page 7 of the instant Office Action). Applicants respectfully point out that the instant claims are directed to polypeptides, not polynucleotides or host cells.

The Examiner acknowledges that "Applicants have taught the polypeptide of SEQ ID NO:59, and have identified specific amino acids as the signal sequence (amino acids 1-16) and the transmembrane domain (amino acids 232-251)." (Page 8 of the instant Office Action). The Examiner asserts, however, that the specification "does not indicate whether the entire protein or a specific region of PRO363 was used in the experiments" and therefore "it is not clear which specific amino acids of PRO363 are critical for each of the disclosed activities." (Page 8 of the instant Office Action). The Examiner concludes that "the claims encompass variants of PRO363 that are inoperative and which the skilled artisan would not know how to use" (Page 9 of the instant Office Action).

Applicants respectfully submit that it is well known in the art that the signal peptide of a protein is not required for function, but serves as a signal for import of the protein into the cell membrane. Once the protein is transported, the signal peptide is cleaved to produce the mature protein. Thus one of ordinary skill in the art would understand that the recited polypeptide of SEQ ID NO:59 lacking its associated signal peptide would have the same activity as the full length SEQ ID NO:59. Accordingly, one of ordinary skill in the art would understand how to use the claimed polypeptide of SEQ ID NO:59 lacking its associated signal peptide, without any undue experimentation.

Further, it is well known in the art that proteins involved in cell signaling, such as proteins that induce chondrocyte redifferentiation, mediate their effects via their extracellular domains, which are positioned to interact with other cells. Accordingly, one of ordinary skill in the art would expect the recited extracellular domain of SEQ ID NO:59, with or without the signal peptide sequence, to share the same chondrocyte redifferentiation activity as the full length SEQ ID NO:59. In addition, the specification discloses that PRO363 has homology to the cell surface protein HCAR, a membrane-bound protein that acts as a receptor for subgroup C of the adenoviruses and subgroup B of the coxsackieviruses (page 4, lines 19-30). The specification further discloses that "extracellular domains derived from the PRO363 polypeptides may be employed therapeutically *in vivo* for lessening the effects of viral infection" (page 199,

lines 37-38). Accordingly, one of ordinary skill in the art would understand how to use the claimed extracellular domains of PRO363, without any undue experimentation.

In addition, without acquiescing to the Examiner's rejection, Applicants submit that Claims 58-62, as amended herein, recite amino acid sequences having at least 80% sequence identity to the polypeptide of SEQ ID NO:59, wherein said polypeptide induces chondrocyte re-differentiation. Thus the recited variant polypeptides all have the same function as the polypeptide of SEQ ID NO:59, and can be used in the same manner, for example, in the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO363 polypeptide induces chondrocyte re-differentiation.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO363 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

The Examiner has asserted that "the art recognizes that a high degree of structural homology may not result in functional homology," and that therefore "the claimed genera of polynucleotides have the potentiality of encoding proteins of many different functions." (Page 9 of the instant Office Action). (Applicants respectfully note that the instant claims are directed to polypeptides, not polynucleotides). In support of this assertion, the Examiner cited articles by Witkowski *et al.* and Seffernick *et al.*

Witkowski *et al.* discloses that a single amino acid substitution transforms a beta-ketoacyl synthase into a malonyl decarboxylase. Applicants note that the authors made mutations at a known active site residue, and even so, of the various substitutions made, only one resulted in the gain of malonyl decarboxylase activity (Abstract). Further, this activity was one which the original enzyme was also capable of, although at a lower rate, and only under specific conditions (Abstract). Thus cases in which a single amino acid change results in altered protein function are clearly highly uncommon. Seffernick *et al.* disclose that two *Pseudomonas* enzymes having 98% sequence identity catalyze different reactions. The authors note, however, that "[i]n this superfamily and in others, members that catalyze different reactions are generally divergent to the extent that amino acid sequence identity is less than 50%" (page 2409, col. 1). The authors further note that "[t]he present finding that proteins with >98% sequence identity catalyze different reactions in different metabolic pathways is **highly exceptional**" (page 2409, col. 1; emphasis added). Thus Seffernick *et al.* confirm that 80% amino acid sequence identity well within the level (of greater than 50%) for which protein function is expected to be conserved.

Further, there is no structural or functional similiarity between the PRO363 polypeptide and the proteins disclosed by Seffernick *et al.* and Witkowski *et al.* The PRO363 polypeptide is a transmembrane protein related to the cell surface viral receptor HCAR. Seffernick *et al.* and Witkowski *et al.*, in contrast, both studied soluble enzymes, in which targeted changes to a few key catalytic residues can alter protein function. In particular, the teachings of Seffernick *et al.* are directed to bacterial enzymes, which undergo unique selection pressures (page 2409, col. 2). Thus there is no basis for extrapolating the results obtained with these structurally and functionally completely different proteins to the predictability of the effect of mutations on the PRO363 polypeptide.

Accordingly, one of ordinary skill in the art would be able to use the guidance provided in the specification, including the listing of conservative amino acid substitutions provided in Table 6, to make nucleic acids encoding variants of SEQ ID NO:59 that would be expected to retain the activity of SEQ ID NO:59 in inducing chondrocyte redifferentiation.

Applicants further note that the claims are not directed to all possible variants having at least 80% amino acid sequence identity to SEQ ID NO:59, but only to those variants which retain the ability of the polypeptide to induce chondrocyte redifferentiation. The specification provides the protocol for a chondrocyte redifferentiation assay, as disclosed in Example 126. It

would be a simple matter for one skilled in the art to test the polypeptides to see if they induce chondrocyte redifferentiation using the methods of Example 126. This would not require undue experimentation.

Finally, the Examiner asserts that "there are no working examples demonstrating that polypeptides less than 100% identical to the polypeptide of SEQ ID NO:59 have any of the disclosed functions." (Page 9 of the instant Office Action). As discussed in the M.P.E.P. §2164.08, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Given that, as discussed above, one of ordinary skill in the art could make and use the claimed variant sequences without any undue experimentation, there is no requirement that the specification provide examples of such variant polypeptides.

The claims currently recite polypeptide sequences associated with a specific biological activity. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[1]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant PRO363 polypeptides having at least 80% identity to SEQ ID NO:59, wherein said polypeptide induces chondrocyte re-differentiation, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

Accordingly, withdrawal of the enablement rejection of Claims 58-62 and 69-70 under 35 U.S.C. §112, first paragraph, is respectfully requested.

---

[1] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

VI. Claim Rejections Under 35 U.S.C. §102

Claims 58-70 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Holtzman *et al.*, U.S. 2002/0055139 A1, with priority to May 14, 1999. Holtzman *et al.* discloses a polypeptide, human A236 protein, that is 100% identical to SEQ ID NO:59, as well as chimeric polypeptides comprising the human A236 protein.

Applicants respectfully submit a Declaration under 37 C.F.R. §1.131 by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood that establishes that Applicants had cloned and sequenced SEQ ID NO:58, and determined the homology of the encoded polypeptide (SEQ ID NO:59) to the cell surface protein HCAR, before the prior art date of May 14, 1999. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

Applicants Need to Disclose Only What is Disclosed in the Cited Reference to Support the Priority Claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(e) rejection over Holtzman *et al.*, the Declaration by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood ("Declaration") simply needs to provide a disclosure commensurate in scope with the disclosure in the prior art document by Holtzman *et al.* to support the priority claim.

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. §1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim.

Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, **an applicant need only show that portion of his or her claimed invention that appears in the cited reference**.

As the Examiner noted, Holtzman *et al.* discloses a polypeptide (human A236 protein) that is 100% identical to SEQ ID NO:59. Holtzman *et al.* discloses that human A236 shares homology to CAR. Although Holtzman *et al.* includes general statements regarding possible uses of the sequence, no specific examples or experimental data are provided regarding the use of human A236.

Applicants respectfully submit that since Holtzman *et al.* only disclose a polypeptide sequence, its encoding nucleic acid sequence, and a sequence homology, without any disclosure to support utility, the Declaration simply needs to show possession of the polypeptide sequence

and its encoding polynucleotide sequence as well as a sequence homology, as disclosed in Holtzman *et al.*, in order to remove the reference as prior art under 35 U.S.C. §102.

Applicants respectfully submit that U.S. Provisional Application Serial No. 60/078,910 filed on March 20, 1998, provides the nucleic acid and amino acid sequences of the PRO363 polypeptide.

The Declaration clearly states that U.S. Provisional Application Serial No. 60/078,910 filed on March 20, 1998 discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:3, which are identical to SEQ ID NO:58 and SEQ ID NO:59, respectively, of the above-identified application. U.S. Provisional Application Serial No. 60/078,910 further discloses that the full length PRO363 polypeptide (SEQ ID NO:59) has significant homology to the cell surface protein HCAR.

Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that U.S. Provisional Application Serial No. 60/078,910 discloses all that the cited prior art discloses.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Holtzman *et al.* is not prior art under §102 since its effective priority date is after the invention by the Applicants for patent.

Accordingly, withdrawal of the rejection of Claim 58-70 under 35 U.S.C. §102(e) as anticipated by Holtzman *et al.* is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C24**).

Respectfully submitted,

Date: November 1, 2005

By: _____
Barrie D. Greene (Reg. No. 46,740)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2164100 v1
10/28/05 9:50 AM (39780.2630)